REMARKS

Favorable reconsideration is respectfully requested in view of the foregoing amendments and following remarks.

Claim 21 which was held to be non-elected by the Examiner has been cancelled without prejudice.

New claims 22-23 have been added which are dependent upon independent claims 12, 13 or 14. Claim 22 is supported on page 3, lines 3-4 of the specification. Claim 23 is supported on page 6, lines 15-17 of the specification.

Turning to the Official Action, claims 12-20 were rejected under 35 USC 102 as anticipated by Trieloff. This ground of rejection is respectfully traversed.

In accordance with the request of the Examiner, a complete copy of the Trieloff document is enclosed, together with an English translation.

As previously explained, this publication was based on an attempt to improve recruitment to the study and contained no result of the study. Consequently, it is clearly non-enabling and no reasonable expectation of success can be shown. The terminology used in this document clearly shows that no one can predict the result of the study.

The following extracts of the English translation of the Trieloff document support this conclusion:

- page 1, paragraph 1: "...preventive therapy with cetirizine...**may** offer protection..."
- page 1, paragraph 2: "...The ETAC study **will** include..."
- page 2, paragraph 2: "The current ETAC study **will attempt**..." and "...Cetirizine **may be expected** to have a preventive function..."
- page 2, paragraph 3: "Pediatricians **still have the chance** to recommend children from their own practice for inclusion of the study".

Accordingly, the cited reference fails to anticipate the claimed methods.

The Examiner further requested copies of the *Minerva Pediatrica* and *Fortschritte der medizin*. Copies of these documents are enclosed, together with their English translations.

Indeed, the first document relates specifically to the risk factors in connection with Atopic Dermatitis, risk factors for the development of food-induced asthma and environmental factors in connection with asthma (see tables I, II & III of document). However, this document does not give any results of a method according to the invention. The only paragraph related to cetirizine reads as follows: "These children **will** be studied **prospectively** until the end of their sixth year. The children **will be** randomized to receive placebo or cetirizine." (see last paragraph, page 6 of English translation of the document).

The second document does not give any results either and only aims at informing parents about an upcoming clinical study. See particularly paragraph 2 of the English translation of this document: "An extensive clinical study (ETAC-early treatment of the Atopic child) now **aims to establish** whether ...". And "Parents whose children suffer from dermatitis can obtain **further information about participation** in the ETAC study from their pediatrician".

On the basis of the above, the claimed invention is not anticipated by any of the documents as they are non-enabling.

In view of the foregoing, it is believed that each ground of rejection set forth in the Official Action has been overcome, and that the application is now in condition for allowance. Accordingly, such allowance is solicited.

Respectfully submitted,

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TRIELOFF, I., TW PADIATRIE (ABSTRACT), PP. 61-62, 1995

Europäische Studie zur Prävention mit Ceterizin

Ist Asthma bei Risikokindern vermeidbar?

Die Entwicklung vom frühkindlichen atopischen Ekzem zum allergischen Asthma bronchiale galt bislang als nahezu unvermeidbar (Abb. 1). Neben der Expositionsprophylaxe – so die Allergene gefunden werden können – bietet die Prävention mit dem modernen Antihistaminikum Ceterizin möglicherweise einen Schutz für Risikokinder. Für Ceterizin ist außer den Substanzklassen-typischen Effekten ein antientzündlicher Wirkmechanismus nachgewiesen.

ETAC-Studie

In einer aktuellen europäischen Multicenter-Studie soll, wie *Prof. Dr. J. Ring*, Hamburg, vor der Fachpresse in Hamburg erklärte, die klinische Erfahrung bestätigt werden und damit die Hypothese, daß die frühzeitige Gabe von Ceterizin die Häufigkeit des frühkindlichen Asthmas oder zumindest den Schweregrad zu verringern vermag. Die ETAC-Studie (Early Treatment of the Atopic Child) wird 700 Kleinkinder einschließen und in 10 europäischen Ländern unter Beteiligung von 6 deutschen Universitätskliniken durchgeführt. Die Laufzeit ist auf 2 Jahre angesetzt, in denen die Kinder entweder Ceterizin erhalten, das als Saft auch von Kleinkindern problemlos eingenommen werden kann, oder entsprechend Placebo.

Allergien nehmen zu – dieser Trend ist weltweit zu beobachten und, wie Ring betonte, durch Genetik allein nicht zu erklären. Über das „Warum" gibt es jedoch nur Hypothesen: Mehr Hausstaub oder ein weniger stimuliertes Immunsystem? Innenraum- oder Außenluft-Schadstoffe?

So früh wie möglich intervenieren!

Außer Zweifel steht aus Sicht von *Prof. Dr. U. Wahn*, Berlin, die vorprogrammierte Allergiker-Karriere (Abb. 2). Die Allergie manifestiert sich bereits im Säuglingsalter. Daher sollte die Prävention noch in der Wiege einsetzen, denn das Kind mit Milchschorf, so Wahn, ist der Asthmatiker von morgen. Der erste Heuschnupfen kann im 3. Lebensjahr auftreten, das erste Asthma bereits zum 5. oder 6. Geburtstag. Frühe Nahrungsmittel-Allergien, die das atopische Ekzem begleiten können, münden dagegen in 9 von 10 Fällen in die Toleranz. Diät ist hier also eine Diät auf Zeit.

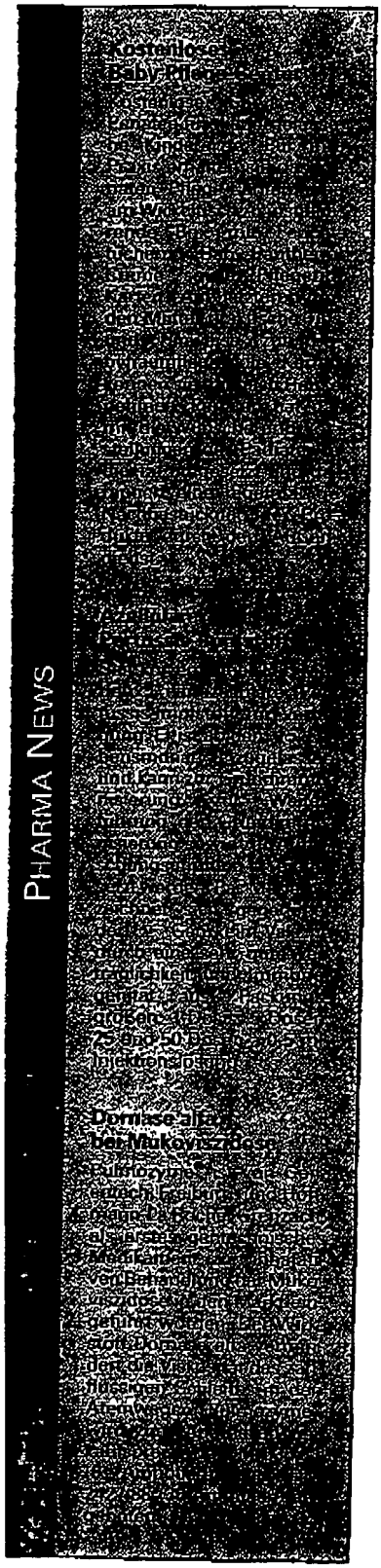
Das Sensibilisierungsrisiko erhöht sich z. B. für Kinder, die in eine hohe Hausstaubmilben-Belastung hineingeboren werden. Aus der Kombination der genetischen Prädisposition mit der allergischen Exposition ergibt sich die Höhe des Risikos (Abb. 3) und damit auch die Entscheidung zur frühen Intervention. Konsequenterweise, so *Prof. Dr. Ch. Rieger*, Bochum, muß bereits während der Schwangerschaft Vorsorge für eine allergenfreie Wohnung getroffen werden, wozu auch eine Berücksichtigung der fast linearen Beziehung zwischen der Zahl der von den Eltern gerauchten Zigaretten und der Asthma-Entwicklung beim Kind zählt. Es ist zu spät, wenn erst zum Zeitpunkt der Geburt die Abschaffung von Haustieren empfohlen wird, denn es dauert Monate, bis Wohnungen von Tier-Allergenen frei werden.

Abbildung 1 Läßt sich mit der präventiven Einnahme von Ceterizin-Saft die Entwicklung des allergischen Asthma bronchiale auf dem Boden eines frühkindlichen atopischen Ekzems vermeiden?

Ceterizin: mögliche präventive Wirkung

Mit der jetzt eingeleiteten ETAC-Studie wird erstmals versucht, den „Switch" vom atopischen Ekzem zum Asthma zu verhindern. Noch gilt es, Aufklärungsarbeit bei den Eltern zu leisten, die ihr Kind in die Studie aufnehmen lassen können. Aufnahmebedingungen sind, daß bei den 1 bis 2 Jahre alten Kindern ein atopisches Ekzem seit mindestens 4 Wochen manifest ist und ein Eltern-

PHARMA NEWS



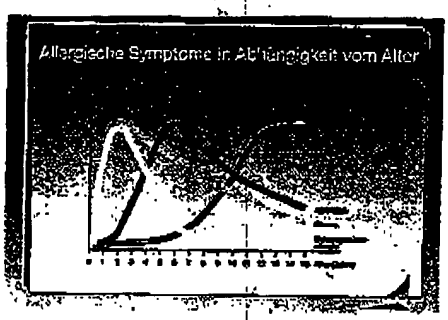


Abbildung 2 Ist der Switch vom atopischen Ekzem zum Asthma, ein typischer Schritt in der Allergiker-Karriere, zu verhindern?

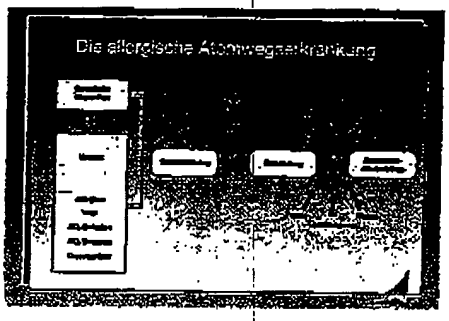


Abbildung 3 Aus der Kombination der genetischen Exposition mit der Allergen-Exposition ergibt sich das Risiko einer allergischen Atemwegserkrankung

teil oder ein Geschwisterkind Neurodermitiker ist oder an Asthma oder allergischer Rhinitis leidet. Das Erkrankungsrisiko unbehandelter Kinder unter dieser Konstellation beträgt 50%. Primäres Studienziel ist es, die Inzidenz des Asthmas bei Risikokindern zu senken. Für Cetirizin ist eine mögliche präventive Funktion im Hinblick auf das allergische Asthma bronchiale zu erwarten, da es, wie *PD Dr. D. Abeck*, Hamburg, erläuterte, durch die nachgewiesene Hemmung der Eosinophilen-Migration über einen deutlichen antientzündlichen Wirkmechanismus verfügt. Cetirizin ist für den Einsatz bei Kindern zugelassen und hat sich als gut verträglich und als sehr sicher erwiesen.

Kinder für die Studie aus Ihrer Praxis!

Noch haben Kinderärzte die Chance, Kinder aus ihrer Praxis für die Aufnahme in die Studie zu empfehlen. Die Betreuung durch den Kinderarzt bleibt in ihrer Kontinuität dabei unbeeinträchtigt.

Dr. Irmin Trieloff, München

Pressekonferenz: Verhinderung des frühkindlichen Asthmas, Hamburg, 14.12.94, Veranstalter UCB

Pneumonien

„Altersabhängige Erreger"

Bei tiefen Atemwegsinfektionen im Erwachsenenalter ist der Erreger in rund 40% der Fälle unbekannt. Bei Kindern liegt dieser Anteil wesentlich höher. Eine Erreger-Diagnostik ist in den meisten Fällen nicht einmal möglich, denn Kinder sind nicht in der Lage, repräsentative Sputum-Proben zu produzieren. Eine sorgfältige Anamnese, Untersuchung und Beobachtung des Krankheitsverlaufes sowie Labor- und Röntgenbefunde geben jedoch manchmal wichtige Hinweise auf die Ätiologie der Infektion.

Von großer Bedeutung ist auch das Alter des betroffenen Kindes. Pneumonien im frühen Säuglingsalter von 3 Wochen bis zu 3 Monaten gehen meist auf Chlamydien zurück. Von diesem Zeitpunkt an bis zum Alter von 2 Jahren dominieren „klassische" Lobär-Pneumonien, hervorgerufen durch Pneumokokken oder Hämophilus influenzae. Die sog. atypischen Lungenentzündungen treten erst nach dem 3. Lebensjahr auf. Sie zeigen einen eher milden Verlauf und sind von der Virus-Pneumonie kaum zu unterscheiden.

Mittel der Wahl zur Behandlung von Infektionen der unteren Atemwege sind Makrolide, z.B. Roxithromycin (Rulid® junior). Dieses moderne Antibiotikum erfaßt zuverlässig alle Leitkeime, ist gut verträglich und muß nur 2mal am Tag eingenommen werden. Bei der „klassischen", hochakuten Lobär-Pneumonie ist dagegen die i.v.-Gabe von Penicillin, Ampicillin oder einem Cephalosporin der 2. Generation indiziert. Exzellente Behandlungserfolge wurden aber auch nach initialer Gabe von oralen Cephalosporinen der 3. Generation (z.B. Cefpodoxim; Orelox® junior), beobachtet. pharmpres

Quelle: Fortbildung für Kinderärzte 1994, eine Veranstaltungsreihe der Firma Albert-Roussel GmbH

ENGLISH TRANSLATION OF TRIELOFF, I., TW PADIATRIE (ABSTRACT), PP. 61-62, 1995

European study on preventive treatment with cetirizine

Is asthma preventable in high-risk children?

The development from infantile atopic dermatitis to allergic bronchial asthma has hitherto been considered almost inevitable (Fig. 1). In addition to exposure prophylaxis – by which means the allergens can be found – preventive therapy with cetirizine, a modern antihistamine, may possibly offer protection for children at risk of developing asthma. In addition to the effects typical of substances of its class, cetirizine has also been found to have an anti-inflammatory mechanism of action.

ETAC study

As Professor J. Ring of Hamburg explained, at a meeting of the medical press held in Hamburg, a European multi-center study is to be carried out to corroborate clinical findings and to confirm the hypothesis that early administration of cetirizine can reduce the incidence of infantile asthma or at least reduce the severity of the condition. The ETAC study (Early Treatment of the Atopic Child) will include 700 infants and be carried out in 10 European countries, with the participation of six German university hospitals. The duration of the study has been set at 2 years, during which time the children will receive either cetirizine, which is easy to administer in the form of a juice, even to small children, or a placebo.

Allergies are becoming increasingly common, and this is a trend that can be observed worldwide. As Professor Ring emphasized, it is a phenomenon that cannot be explained by genetic factors alone. However, as regards the question of "why", only hypotheses are available: more house dust, or less stimulation of the immune system? Indoor or outdoor pollutants?

Intervention as early as possible

In the opinion of Professor U. Wahn of Berlin, there can be no doubt that the history of the allergy sufferer's condition is preprogammed (Fig. 2). Allergies manifest themselves even in early infancy. For this reason, prevention should begin as early as the cradle, since, according to Professor Wahn, the child with cradle cap is tomorrow's asthma sufferer. The first episode of hay fever can occur in the 3rd year of life, and the first attack of asthma as early as the 5th or 6th year. By contrast, early food allergies, which may accompany atopic dermatitis, develop into tolerance in 9 out of 10 cases. Here, therefore, time is all important to diet.

The risk of sensitization increases, for example, in children born into an environment with a large population of house dust mites. A combination of genetic predisposition and of

exposure to allergens (Fig. 3) determines the level of risk and, consequently, the decision to intervene at an early stage. For this reason, according to Professor C. Rieger of Bochum, precautionary measures must be taken during pregnancy in order to ensure an allergen-free home environment, and in this respect account must also be taken of the almost linear relationship between the number of cigarettes smoked by the parents and the development of asthma in the child. Removing household pets when the child is born is to act too late, since it takes months to rid households of animal allergens.

Cetirizine: possible preventive action

The current ETAC study will attempt for the first time to prevent the "switch" from atopic dermatitis to asthma. Work still has to be done on providing information to parents able to enter their children in the study. Inclusion conditions are that the children who are aged from 1 to 2 year have had atopic dermatitis for a period of at least 4 weeks and have a parent or sibling who suffers from neurodermatitis, asthma or allergic rhinitis. There is a 50% risk of the disease developing in untreated children in this group. The primary aim of the study is to reduce the incidence of asthma in high-risk children. Cetirizine may be expected to have a preventive function in respect of allergic bronchial asthma, since, as Doctor D. Abeck of Hamburg explained, its proven inhibition of eosinophil migration means it has an important anti-inflammatory mechanism of action. Cetirizine is approved for use in children and has proven to be well tolerated and very safe.

Children from your practice can take part

Pediatricians still have the chance to recommend children from their own practice for inclusion in the study. The continuity of the medical care provided by the pediatrician remains unaffected.

Doctor Irmin Trieloff, Munich

Press conference: Prevention of infantile asthma. Hamburg, 12.14.94. Organized by UCB

Figure 1: Can the development of allergic bronchial asthma, following on from infantile atopic dermatitis, be prevented by administration of cetirizine juice?

Figure 2: Is the switch from atopic deramtitis to asthma a typical step in the allergy sufferer's history) preventable?
Box: Allergic symptoms as a function of age

Figure 3: A combination of genetic factors and exposure to allergens determines the risk of allergic respiratory disease.
Box: Allergic respiratory disease

L. BUSINCO ET AL., MINERVA PEDIATRICA, VOL. 49, NO. 10, PP. 477-481, 1997

MINERVA PEDIATR 1997;49:477-81

Dalla dermatite atopica all'asma

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From eczema to asthma.

Atopic dermatitis (AD) is the most common chronic skin disorder in infancy and childhood and is the main hallmark of atopic constitution. The disease is multifactorial, and although genetic predisposition is certainly a prerequisite, a number of enviromental factors modulate the phenotypic expression of AD. The majority of affected children shows IgE sensitisation towards a large variety of foods and aeroallergens. Since at least 1600, it has been recognized that patients with AD have a high predisposition to develop asthma. Recent epidemiological studies show that AD is commonly seen in individuals from families with a history of asthma. In addition, in population where asthma is uncommon, AD is also uncommon. The sex distribution of AD and asthma is the same, with boys affected significantly more often by these two atopic diseases and in similar proportions. The ETAC project (Early Treatment of the Atopic Child) is a large multicenter, multi-national, double blind, placebo controlled, randomised trial. The main objective of the study is to stop the progression from AD to asthma in young children with AD using early therapeutic intervention with Cetirizine and the second objective is to investigate the main risk factors for the onset of asthma. The results of this study indicate that exposure to potent allergens such as cat or mite significantly increased the risk of sensitisation to these allergens. Prolonged breast feeding was associated with a lowest sensitisation rate to cow milk proteins and to egg. Therefore environmental factors seem to play a crucial role in IgE sensitisation in children with AD.

Key words: Dermatitis atopic - Asthma - Risk factors.

Pervenuto il 23 luglio 1997.
Accettato il 18 settembre 1997.

Indirizzo per la richiesta di estratti: L. Businco - Clinica Pediatrica, Viale Regina Elena, 324 - 00161 Roma.

La dermatite atopica (DA) del bambino, nonostante sia una affezione frequente e conosciuta sin dall'antichità, è stata trascurata dagli allergologi pediatri fino ad alcuni anni orsono. Tale «negligenza» è probabilmente giustificata dal decorso favorevole della DA nella maggior parte dei casi. Infatti, una grande percentuale dei bambini affetti da DA guarisce spontaneamente o migliora notevolmente nel corso dei primi anni di vita.

Da quando, però, specie negli ultimi anni, l'asma è divenuto sempre più frequente e talora grave nel bambino, la DA ha attratto l'interesse dei ricercatori. Infatti la particolare storia naturale di questa malattia, rappresenta un modello ideale per studiare i fattori di rischio per lo sviluppo di asma.

È stato dimostrato da numerosi studi pro-

spettici che fino all'80% dei bambini affetti da DA presenteranno asma nel corso dei primi dieci anni di vita. Inoltre, l'asma che colpisce bambini affetti da DA ha un decorso più grave e più cronico rispetto ai bambini non affetti da questa patologia.

Cenni storici

Il termine dermatite atopica è stato introdotto nel 1933 da Hill e Sulzberger che già mettevano in correlazione questa patologia cutanea con manifestazioni allergiche di tipo respiratorio [1].

Rimaneva comunque da dimostrare che la DA non fosse semplicemente un processo infiammatorio cronico della cute frequentemente associato con asma o rinite, ma una malattia su base allergica.

Nel 1953 Purdy [2] studiando un gruppo di pazienti che avevano avuto eczema infantile, riscontrò nel 51% dei casi la comparsa di sintomi respiratori, e precisamente asma nel 40% dei casi e sporadici episodi di broncospasmo nell'11% dei casi. Nel 1965 Pastemak [3] analizzando l'incidenza di asma in bambini con DA, poneva il problema in termini statistici, individuando già nella gravità della dermatite, nell'età di insorgenza e nella familiarità per asma e malattie allergiche, importanti fattori predittivi per la futura insorgenza di asma.

Queille-Roussel *et al.* hanno riscontrato, studiando 500 pazienti con dermatite atopica, di età mediana pari a 5,7, lo sviluppo di asma, dopo il compimento del sesto anno di vita, nel 34% dei casi [4]. In un interessante studio condotto su 955 adulti che avevano presentato dermatite atopica in età pediatrica, Rysted ha riscontrato la comparsa di asma nel 32% dei casi [5].

Recenti studi epidemiologici mostrano che la DA è presente frequentemente in individui provenienti da famiglie con una storia di asma e che la DA è rara in quelle popolazioni dove l'asma non è una malattia comune [6].

La correlazione fra DA e asma sembra essere ulteriormente rafforzata dall'evidenza che entrambe le patologie hanno la stessa distribuzione riguardo al sesso, prevalendo entrambe nel sesso maschile [6].

Ma soltanto studiando profondamente il meccanismo patogenetico alla base delle due malattie allergiche, si può vedere chiaramente la correlazione esistente fra DA e asma, in primo luogo come diversa collocazione d'organo dei medesimi meccanismi immunopatologici, in secondo luogo di stretta consequenzialità temporale.

La predisposizione genetica allo sviluppo di una risposta IgE mediata sembra essere la stessa sia nei pazienti con asma che in quelli con DA. Partendo dal presupposto che le due patologie debbano essere considerate a carattere multifattoriale, sicuramente molti geni comuni condizionano a vari livelli lo sviluppo della flogosi allergica. L'amplificazione della risposta Th2 e il conseguente aumento di IL4, IL5, IL13, GM-CSF e IL10 sono fattori che esaltano la produzione di IgE e coinvolgono nella flogosi allergica locale altre cellule tra cui gli eosinofili. Queste cellule attivate sono responsabili, attraverso la produzione di ECP e MBP, del danno tessutale. La flogosi allergica, che una volta innescata è in grado di mantenersi cronicamente, è un elemento in comune tra DA e altre malattie allergiche, tra cui l'asma [7], mentre la diversa espressione delle molecole di adesione rende possibile l'afflusso di linfociti ed eosinofili a livello cutaneo, caratterizzando la specificità d'organo, nell'ambito di un comune processo fisiopatologico.

Fattori di rischio per lo sviluppo di asma

La DA può essere considerata come un esperimento della natura che ci permette di individuare e studiare i fattori di rischio e la sensibilizzazione allergica per lo sviluppo di asma nei primi anni di vita. Quindi individuare e studiare questi fattori, coinvolti nello sviluppo di asma nei bambini con DA, ci permetterà di praticare una valida prevenzione (tab. I).

Da uno studio di Gillet si evidenzia stretta correlazione (96%) tra DA grave ed allergia alimentare e legame significativo tra DA grave e sensibilizzazione agli allergeni inalanti [8].

TABELLA I. — *Fattori di rischio per lo sviluppo di asma in bambini con dermatite atopica.*

Sesso maschile
Storia familiare positiva per asma
Esposizione al fumo passivo
Sensibilizzazione ad allergeni inalanti nel I anno di vita
Test cutanei positivi all'uovo

TABELLA II. — *Fattori di rischio per sviluppo di asma indotto da alimenti in bambini con dermatite atopica.*

Elevati livelli di IgE
Associazione di altre manifestazioni di allergia alimentare
orticaria
angioedema
disturbi gastrointestinali
Test cutanei e/o IgE specifiche fortemente positivi per alimenti

Gillet individua, ulteriormente, nella presenza di *allergia alimentare* un fattore prognostico negativo per la gravità della DA e un *importante fattore predittivo per lo sviluppo dei sintomi respiratori* [8].

La relazione tra DA e allergia alimentare è stata ampliamente confermata da studi compiuti negli ultimi anni basati sull'impiego di diete di eliminazione o di test di provocazione orale. Questi studi mostrano come l'allergia alimentare costituisca un ruolo patogenetico rilevante in almeno il 50% dei bambini con DA [9 10].

Inoltre studi in doppio cieco contro placebo descrivono un netto miglioramento dei sintomi dopo l'eliminazione dalla dieta degli alimenti incriminati [11]. Da studi che ricalcano la stessa metodologia, appare chiara la correlazione tra ingestione o inalazione di alimenti ed asma, in bambini con allergia alimentare, storia di DA ed elevati livelli di IgE nel sangue [12] (tab. II).

Sebbene non ci sia uniformità di pensiero nell'associazione tra DA e allergia alimentare, certo è che i casi più gravi di DA sono strettamente correlati all'alterazione dei principali parametri di valutazione allergologica (Skin Prick Test, dosaggio delle IgE specifiche) sia per allergeni alimentari che per allergeni inalanti.

Iperreattività bronchiale aspecifica e DA

Per *iperreattività bronchiale aspecifica* (IBA) si intende l'abnorme risposta delle vie aeree in seguito a svariati stimoli, sia chimici quali istamina e metacolina, che naturali come esercizio fisico, iperventilazione di aria fredda o particolarmente secca, aerosol di acqua distillata.

Si tratta di stimoli aspecifici attivi in tutti i pazienti con asma sia atopici che non.

Quando si verifica una risposta di tipo broncocostrittivo a concentrazione di sostanza 10-1000 volte inferiore a quella necessaria a provocare broncospasmo nei soggetti normali, si parla di IBA.

La IBA viene studiata valutando la dose (PD20) e la concentrazione (PC20) di sostanza in grado di provocare la caduta del FEV1 del 20% rispetto al valore basale.

I meccanismi responsabili dell'IBA non sono ancora conosciuti. Tuttavia viene comunque ipotizzata una riduzione di calibro delle vie aeree, una ipersensibilità della muscolatura liscia bronchiale, un'aumentata sensibilità dei recettori presenti sulle fibre nervose a livello epiteliale e uno squilibrio a carico dei neurotrasmettitori del sistema nervoso autonomo delle vie aeree, e del loro metabolismo.

Sebbene non esistano dati conclusivi sull'identificazione dei geni coinvolti nell'IBA molte evidenze vedono l'iperreattività bronchiale aspecifica significativamente associata all'atopia.

È stato dimostrato che i bambini con DA presentano, prima della comparsa di asma, aumento della *iperreattività bronchiale aspecifica* [13 14]. Ciò può essere diagnosticato dal pediatra nella pratica clinica quotidiana, quando i bambini con DA, presentano in corso di infezioni virali respiratorie, o dopo una corsa, o dopo una risata prolungata, broncospasmo.

Il ruolo degli allergeni inalanti

Un ruolo chiave nel mantenimento della flogosi allergica, che si può manifestare contemporaneamente a livello cutaneo e respiratorio, o consequenzialmente nel tempo, è rappresentato da *fattori ambientali* ed in

modo particolare dalla *sensibilizzazione all'acaro della polvere*, in un primo momento ed ai *pollini* successivamente.

Alcuni studi clinici mettono in relazione la positività al patch test per acaro, pollini, muffe, peli di animali ed esacerbazione dei sintomi di dermatite atopica al contatto con i seguenti allergeni [15 16].

Dati di laboratorio supportano il ruolo degli allergeni inalanti come fattori in grado di modulare e mantenere la flogosi allergica locale [17 18].

Negli ultimi dieci anni è stato studiato in particolare il ruolo dell'acaro della polvere di casa, anche nei pazienti con DA senza asma, cercando di evidenziare, attraverso l'uso del patch test, il contributo dell'allergene Der p1 nell'alimentare la lesione eczematosa [19]. Inoltre frequentemente pazienti con DA che non presentano ancora alcun sintomo respiratorio, mostrano alti livelli di IgE e IgG contro il Der p1.

Recentemente, altri A., hanno messo in correlazione la esacerbazione dei sintomi cutanei in seguito alla inalazione del Der p1 nei pazienti che possedevano alti livelli di IgE specifiche contro l'acaro della polvere, suggerendo una possibile correlazione tra reazione bronchiale e cutanea [20].

La profilassi ambientale contro l'acaro della polvere di casa, quindi, assume un ruolo centrale e ci sembra doverosa in bambini con DA, con SPT positivi ed alti livelli di IgE contro il Der p1, per prevenire lo sviluppo di asma.

Mentre la presenza di un animale in casa, in Italia, non sembra essere correlata allo sviluppo di asma, un ruolo sicuramente più rilevante è rappresentato dalla *presenza di moquette* e dall'*esposizione al fumo passivo* nell'ambiente domestico (tab. III). Tutto ciò emerge dai dati preliminari di un importante studio multicentrico internazionale, a cui partecipano 13 paesi europei più il Canada, denominato progetto ETAC (Early Treatment of Atopic Child) realizzato con l'intento di studiare i fattori di rischio per lo sviluppo di asma in bambini con DA e per valutare la possibile efficacia terapeutica della cetirizina, in bambini con DA.

Sono stati arruolati 817 bambini, figli di genitori allergici, affetti da DA, con storia negativa per asma, di età inferiore al secondo anno di vita.

TABELLA III. — *Prevenzione dell'asma in bambini con dermatite atopica.*

Evitare l'esposizione al fumo passivo
Ridurre le concentrazioni di acari nell'abitazione
Ridurre l'umidità nell'abitazione
Aumentare la ventilazione nell'abitazione
Prevenzione farmacologica
Immunoterapia specifica in presenza di rinite e sensibilizzazione ad allergeni (acari, pollini)

Questi bambini saranno studiati prospetticamente fino al compimento del sesto anno di età. I bambini in maniera randomizzata ricevono placebo o cetirizina.

La valutazione dei dati allergologici uniti alle caratteristiche dell'ambiente, in cui questi bambini vivono, ha fornito dei dati di estremo interesse.

È stato così dimostrato che i bambini che hanno moquette in camera da letto presentano sensibilizzazione all'acaro della polvere in maniera altamente significativa rispetto a quei bambini che invece non ne hanno.

Infatti, concordemente ad ogni previsione, i bambini inglesi che avevano moquette in camera da letto nel 95% dei casi, presentavano sensibilizzazione all'acaro della polvere di casa significativamente superiore a quelli degli altri paesi europei dove la diffusione di moquette era sicuramente inferiore.

Inoltre è emerso che bambini esposti al fumo passivo dei genitori presentano livelli di IgE più elevati e sensibilizzazione allergica più frequente verso svariati allergeni, inclusi quelli alimentari, in una percentuale compresa tra il 30 ed il 50% dei casi.

La presenza di un animale in casa, in questo caso di un gatto, non sembra essere significativamente associata, nel bambino italiano, con lo sviluppo di asma. Questo dato contrasta con quello dei paesi del nord-Europa e può essere spiegato considerando le particolari condizioni climatiche del nostro Paese, dove spesso l'animale domestico permane per lunghi periodi fuori dall'abitazione.

È molto interessante seguire questi bambini fino al sesto anno di età per valutare il ruolo svolto da questi fattori ambientali e dalla sensibilizzazione precoce agli allergeni

nello sviluppo di asma e valutare l'azione profilattica della cetirizina.

In conclusione la DA rappresenta come già sottolineato un modello ideale per studiare la sensibilizzazione allergica nei primi anni di vita e lo sviluppo di asma.

Non vi è dubbio che l'ambiente abbia un'importanza chiave nel favorire sensibilizzazione allergica e quindi la comparsa di allergia respiratoria.

Misure preventive ambientali dovrebbero essere indirizzate a tutti i bambini affetti da DA.

Queste misure prevedono una scrupolosa profilassi per l'acaro della polvere, con particolare attenzione alla camera da letto dove il bambino trascorre sicuramente buona parte della sua giornata, il divieto assoluto di fumo in tutti gli ambienti frequentati dal bambino e il possibile impiego di farmaci preventivi dopo attenta valutazione specialistica.

Riassunto

La dermatite atopica (DA) è la più comune malattia cronica della cute nell'infanzia e nell'adolescenza ed è il principale segno di costituzione atopica. La malattia è multifattoriale, e oltre alla predisposizione genetica, che è sicuramente un prerequisito, numerosi fattori ambientali ne modulano l'espressione fenotipica. Infatti molti bambini affetti presentano una sensibilizzazione IgE-mediata verso numerosi alimenti ed inalanti ambientali. Fin dal 1600 è stato osservato che pazienti con DA avevano un'elevata probabilità a sviluppare asma. Recenti studi epidemiologici mostrano che la DA è presente frequentemente in individui provenienti da famiglie con una storia di asma e che la DA è rara in quelle popolazioni dove l'asma non è una malattia comune. La correlazione fra DA e asma sembra essere ulteriormente rafforzata dall'evidenza che entrambe le patologie hanno la stessa distribuzione riguardo al sesso, prevalendo entrambe nel sesso maschile. Il progetto ETAC è un trial randomizzato, internazionale, multicentrico, in doppio cieco contro placebo. Il principale obiettivo di questo studio è di impedire, con precoce terapia a base di Cetirizina, l'insorgenza di asma in bambini con DA; il secondo obiettivo è quello di indagare i fattori di rischio per lo sviluppo di asma. I dati preliminari di questo studio hanno confermato l'importante ruolo dell'ambiente nel condizionare la sensibilizzazione allergica nel bambino con DA. Infatti l'esposizione nelle prime epoche della vita a potenti allergeni, come l'acaro della polvere, il gatto, l'uovo e il latte vaccino, rappresenta un fattore di rischio significativo per la sensibilizzazione allergica.

Parole chiave: Dermatite atopica - Asma - Asma, fattori di rischio.

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REVIEWS

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From eczema to asthma

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Atopic dermatitis (AD) is the most common chronic skin disorder in infancy and childhood and is the main hallmark of an atopic constitution. The disease is multifactorial and although genetic predisposition is certainly a prerequisite, a number of environmental factors modulate the phenotypic expression of AD. The majority of affected children show IgE sensitisation towards a large variety of foods and aero-allergens. Since at least 1600, it has been recognised that patients with AD have a high predisposition to develop asthma. Recent epidemiological studies show that AD is commonly seen in individuals from families with a history of asthma. In addition, in populations where asthma is uncommon, AD is also uncommon. The sex distribution of AD and asthma is the same, with boys affected significantly more often by these two atopic diseases and in similar proportions. The ETAC project (Early Treatment of the Atopic Child) is a large multicentre, multinational, double-blind, placebo-controlled, randomised trial. The main objective of the study is to stop the progression from AD to asthma in young children with AD using early therapeutic intervention with cetirizine and the second objective is to investigate the main risk factors for the onset of asthma. The results of the study indicate that exposure to potent allergens such as cat or mite significantly increased the risk of sensitisation to these allergens. Prolonged breast-feeding was associated with the lowest

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sensitisation rate to cow milk proteins and egg. Therefore, environmental factors seem to play a crucial role in IgE sensitisation in children with AD.
Keywords: **Dermatitis atopic - Asthma - Risk factors.**

Despite being a common condition and one that has been known since ancient times, atopic dermatitis (AD) in children was ignored by paediatric allergy specialists until a few years ago. This 'negligence' is probably explained by the favourable outcome of AD in the majority of cases. In fact, a large percentage of children suffering from AD are cured spontaneously or improve considerably during the first few years of life.

However, because asthma has become increasingly more common and sometimes severe in children, particularly in the last few years, AD has attracted the interest of researchers. In fact, the specific natural history of this disease constitutes an ideal model for studying the risk factors for the development of asthma.

Numerous prospective studies have shown that up to 80% of children suffering from AD will develop asthma in the course of the first 10 years of life. In addition, asthma that affects children suffering from AD has a more severe and a more chronic course than in children who do not suffer from this disease.

Historical outlines

The term atopic dermatitis was introduced in 1933 by Hill and Sulzberger, who already associated this skin condition with allergic respiratory manifestations[1].

However, it remained to be shown that AD was not simply a chronic inflammatory process of the skin frequently associated with asthma or rhinitis, but a disease with an allergic basis.

In 1953, Purdy[2], studying a group of patients who had suffered from infantile eczema, found the occurrence of respiratory symptoms in 51% of cases, and in particular asthma in 40% of cases and sporadic episodes of bronchospasm in 11%. In 1965, Pasternak[3], analysing the incidence of asthma in children with AD, presented the problem in statistical terms, identifying in the severity of the dermatitis, the age of onset and the family history of asthma and allergic diseases important predictive factors for the future onset of asthma.

Queille-Roussel *et al.*, studying 500 patients with atopic dermatitis with a mean age of 5.7 years, found the development of asthma by the age of 6 in 34% of cases[4]. In an interesting study conducted in 955 adults suffering from atopic dermatitis in childhood, Rysted found the occurrence of asthma in 32% of cases[5].

Recent epidemiological studies show that AD is frequently present in individuals from families with a history of asthma and that AD is rare in those populations in which asthma is not a common disease[6].

The correlation between AD and asthma appears to be further strengthened by the evidence that both diseases have the same sex distribution, with a greater prevalence of males in both[6].

However, only by studying in depth the pathogenetic mechanism behind the two allergic diseases is it possible to see clearly the correlation between AD and asthma, in the first place as a different organ localization for the same pathological mechanisms, and in the second place with a strict chronological sequence.

The genetic predisposition to the development of an IgE-mediated response appears to be the same in both patients with asthma and those with AD. Starting from the assumption that the two diseases must be considered multifactorial, many common genes certainly determine the development of allergic inflammation at various levels. The amplification of the Th2 response and the subsequent increase in IL4, IL5, IL13, GM-CSF and IL10 are factors which intensify the production of IgE and involve other cells, including eosinophils, in the local allergic inflammation. These activated cells are responsible for tissue damage through the production of ECP and MBP. Allergic inflammation, which, once triggered, is capable of maintaining itself chronically, is common to AD and other allergic diseases, including asthma[7], while the different expression of adhesion molecules permits the afflux of lymphocytes and eosinophils in the skin, determining the organ specificity within the context of a common pathophysiological process.

Risk factors for the development of asthma

AD may be considered an experiment by nature, making it possible to identify and study the risk factors and the allergic sensitisation for the development of asthma in the early years of life. Thus, identifying and studying these factors involved in the development of asthma in children with AD will make it possible to implement valid prevention (table I).

A study by Guillet showed a close correlation (96%) between severe AD and food allergy and a significant link between severe AD and sensitisation to inhalant allergens[8]. Guillet subsequently identified a negative prognostic factor for the severity of AD in the presence of *food allergy* and an *important predictive factor for the development of respiratory symptoms*[8].

Table I - *Risk factors for the development of asthma in children with atopic dermatitis.*

Male sex
Positive family history of asthma
Exposure to passive smoking
Sensitisation to inhalant allergens in the first year of life
Positive skin tests for egg

The relationship between AD and food allergy has been substantially confirmed by studies conducted in the last few years based on the use of an elimination diet or oral challenge tests. The studies show how food allergy plays a relevant pathogenetic role in at least 50% of children with AD[9,10].

In addition, double-blind, placebo-controlled studies describe a marked improvement in symptoms after the elimination of the incriminated food from the diet[11]. Studies following the same methodology demonstrate the correlation between the ingestion or inhalation of foods and asthma in children with food allergy, a history of AD and high levels of IgE in the blood[12] (table II).

Table II. - *Risk factors for the development of food-induced asthma in children with atopic dermatitis.*

High levels of IgE
Association with other manifestations of food allergy
urticaria
angio-oedema
gastro-intestinal disorders
Skin tests and/or specific IgE highly positive for food

Although there is no uniform opinion about the association between AD and food allergy, it is certain that the most serious cases of AD are closely correlated with impairment of the main parameters used in allergy evaluation (skin prick test, assay of specific IgE), both for food allergens and for inhalant allergens.

Non-specific bronchial hyperreactivity and AD

By *non-specific bronchial hyperreactivity* (NBH) is understood the abnormal response of the airways to various stimuli, both chemical such as histamine and

metacholine, and natural such as physical exercise, hyperventilation of cold or particularly dry air and a distilled water spray.

These are a specific stimuli which are active in all patients with asthma, whether atopic or not.

When a bronchoconstrictive type of response is observed at a substance concentration 10-1000 times lower than that necessary to cause bronchospasm in normal subjects, this is referred to as NBH.

NBH is studied by evaluating the dose (PD20) and the concentration (PC20) of a substance capable of causing a 20% fall in FEV1 from the baseline value.

The mechanisms responsible for NBH are still not yet known. However, a reduction in airways calibre, hypersensitivity of bronchial smooth muscle, increased sensitivity of the receptors present in the nerve fibres in the epithelium and an imbalance in the neurotransmitters of the autonomic nervous system of the airways and their metabolism are postulated.

Although there are no conclusive data about the identification of the genes involved in NBH, there is considerable evidence to show that non-specific bronchial hyperreactivity is significantly associated with atopy.

It has been shown that children with AD exhibit an increase in *non-specific bronchial hyperreactivity* before the onset of asthma[13,14]. This can be diagnosed by the paediatrician in daily clinical practice when children with AD develop bronchospasm during viral respiratory infections or after running or after a prolonged episode of laughter.

The role of inhalant allergens

A key role in the maintenance of allergic inflammation, which may manifest itself simultaneously at a cutaneous and at a respiratory level or successively over time, is played by *environmental factors* and particularly by *sensitisation to dust mite* initially and to *pollens* subsequently.

Some clinical studies correlate positive responses to the patch test for dust mite, pollen, moulds and animal hair with exacerbation of the symptoms of atopic dermatitis on contact with these allergens[15,16].

Laboratory data support the role of inhalant allergens as factors capable of modulating and maintaining local allergic inflammation[17,18].

In the last 10 years, the role of the house dust mite in particular has been studied, including in patients with AD but without asthma, in an attempt to demonstrate the contribution of the allergen Der p1 to promotion of the eczematic

lesion through the use of the patch test[19]. In addition, patients with AD who do not yet exhibit any respiratory symptoms frequently have high levels of IgE and IgG to Der p1.

Recently, other authors have shown a correlation between the exacerbation of cutaneous symptoms following inhalation of Der p1 in patients possessing high levels of specific IgE against dust mite, suggesting a possible correlation between the bronchial and the cutaneous reaction[20].

Environmental prophylaxis against house dust mite thus assumes a central role and appears appropriate in children with AD with positive SPT and high levels of IgE against Der p1 in order to prevent the development of asthma.

While the presence of an animal in the home in Italy does not appear to be correlated with the development of asthma, a definitely more relevant role is played by the *presence of carpets* and *exposure to passive smoking* in the home environment (table III). All this emerges from the preliminary data from an important international multicentre study involving 13 European countries plus Canada, known as the ETAC project (Early Treatment of the Atopic Child) conducted with the intention of studying the risk factors for the development of asthma in children with AD and evaluating the possible therapeutic efficacy of cetirizine in children with AD.

Table III. - *Prevention of asthma in children with atopic dermatitis.*

Avoid exposure to passive smoking
Reduce mite concentrations in the home
Reduce humidity in the home
Increase ventilation in the home
Pharmacological prevention
Specific immunotherapy in the presence of rhinitis and sensitisation to allergens (mites, pollen)

817 children of allergic parents suffering from AD with a negative history of asthma and aged less than two years old were included.

These children will be studied prospectively until the end of their sixth year. The children will be randomised to receive placebo or cetirizine.

The evaluation of the allergy data together with the characteristics of the environment in which these children live have provided data of considerable interest.

It has thus been demonstrated that children with carpets in their bedrooms are highly significantly sensitised to dust mite compared to children who do not have a carpet.

In fact, as was to be expected, English children who had carpets in their bedroom in 95% of cases were significantly more sensitised to house dust mite than those in other European countries where carpets were certainly less widespread.

In addition, it has emerged that children exposed to passive smoking by their parents have higher levels of IgE and more frequent allergic sensitisation to various allergens, including food, in between 30 and 50% of cases.

The presence of an animal in the home, in this case a cat, does not appear to be significantly associated in Italian children with the development of asthma. This runs counter to the experience in Northern European countries and may be explained in terms of the specific climatic conditions of our country, where the domestic animal often remains out of doors for long periods.

It is very interesting to follow these children up to the age of 6 years to evaluate the role played by these environmental factors and early sensitisation to allergens in the development of asthma and to evaluate the prophylactic action of cetirizine.

In conclusion, as already emphasised, AD represents an ideal model for studying allergic sensitisation in the first years of life and the development of asthma.

There is no doubt that the environment plays a key role in promoting allergic sensitisation and hence in the development of respiratory allergy.

Environmental preventive measures should be adopted for all children suffering from AD.

These measures required strict prophylaxis of dust mite with particular attention to the bedroom where the child certainly spends a good part of their day, an absolute ban on smoking in all the environments frequented by the child and the possible use of preventive drugs following careful specialist evaluation.

Translator's Report/Comments

Your ref: IPD/0402-041 **Your order of (date):** 6/2/04

In translating the above text we have noted the following apparent errors/unclear passages which we have corrected or amended:

Page/para/line*	Comment
P478 Column 2 para 5	Gillet should read Guillet and has been translated as such.

* This identification refers to the source text. Please note that the first paragraph is taken to be, where relevant, the end portion of a paragraph starting on the preceding page. Where the paragraph is stated, the line number relates to the particular paragraph. Where no paragraph is stated, the line number refers to the page margin line number.

FORTSCHRITTE DER MEDIZIN, VOL. 113, P. 42, 1985

PDED96KD101

ANONYME

26306

Frühzeitige Allergiebehandlung soll Asthma verhindern

Allergische Erkrankungen sind häufig im Sinne einer Progression miteinander verbunden, d. h., Nahrungsmittelallergien im Säuglingsalter führen zu atopischer Dermatitis, die Erkrankung kann auf die oberen Atemwege übergreifen und zur Rhinitis führen; etwa ein Drittel dieser Patienten wiederum entwickelt im späteren Leben Asthma bronchiale. Für die Praxis bedeutet dies, daß die zugrundeliegende immunologische Reaktion sehr früh und über die Symptomatik hinaus behandelt werden sollte.

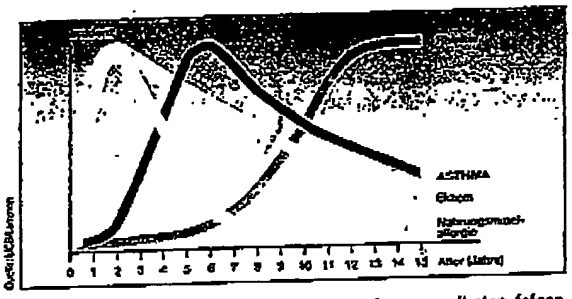
In einer umfangreichen klinischen Untersuchung (ETAC = Early Treatment of the Atopic Child) soll jetzt geklärt werden, ob die frühzeitige Behandlung von asthmagefährdeten Kindern die Krankheit unterbinden oder zumindest deren Ausbruch verzögern und ihre Symptome mildern kann. Die ETAC-Studie ist ein randomisierter, doppelblinder und plazebokontrollierter Test unter Verwendung von Cetirizin als pharmakologisches Agens. Cetirizin wurde gewählt, weil es mehrere Inhibitionseffekte auf die zugrundeliegenden Entzündungsvorgänge ausübt. Es wurden folgende Kriterien für eine asthmatische Gefährdung und damit für die Teilnahme an der Studie erstellt:

▷ Mindestens ein Elternteil muß eine atopische Krankheitsgeschichte aufweisen;

▷ das Kleinkind selbst muß deutlich Symptome einer atopischen Dermatitis zeigen;

▷ Das Kleinkind ist noch asthmafrei.

Eltern, deren Kleinkinder an atopischer Dermatitis leiden, können sich hinsichtlich der Teilnahme an der ETAC-Studie bei ihrem Kinderarzt informieren. C. L



Quelle: UCB-Abbott

Die Altersphasen, in denen allergische Erkrankungen auftreten, folgen einem gut dokumentierten Muster.

Nach einer Pressekonferenz der UCB Pharma GmbH.

ENGLISH TRANSLATION OF FORTSCHRITTE DER MEDIZIN, VOL. 113, P. 42, 1985

Early allergy treatment should prevent asthma

Allergic diseases are often interconnected in the sense of a progression, i.e. food allergies in early infancy lead to atopic dermatitis, and the disease can pass to the upper airways and lead to rhinitis. About one third of these patients develop bronchial asthma in later life. This means that the underlying immunological reaction should be treated at a very early stage and on the basis of the symptoms.

An extensive clinical study (ETAC = Early Treatment of the Atopic Child) now aims to establish whether early treatment of children at risk of developing asthma can suppress the disease or at least delay its onset and alleviate its symptoms. The ETAC study is a randomized, double-blind, placebo-controlled trial using cetirizine as pharmacological agent. Cetirizine was chosen because of the many inhibitory effects it has on the underlying inflammatory processes. The criteria drawn up for subjects at risk of developing asthma and thus able to participate in the study were as follows:

- at least one parent must have a history of atopic disease;
- the infant himself/herself must show clear symptoms of atopic dermatitis;
- the infant is still free from asthma.

Parents whose children suffer from atopic dermatitis can obtain further information about participation in the ETAC study from their pediatrician.

C.L.

From a press conference organized by UCB Pharma GmbH

Caption

The ages at which allergic diseases occur follow a well-documented pattern.